```
Human caspase-1          ---------------------------------------- MADKVLKEKRKLFIRSMG
Human caspase-13[a]      ---------------------------------------- MAEDKHNKNPLKMLESLG
Human caspase-4          ---------------------------------------- MAEGNHRKKPLKVLESLG
Human caspase-5          MFKGILQSGLDNFVINHMLKNNVAGQTSIQTLVPNTDQKSTSVKKDNHKKKTVKMLEYLG
Human caspase-12         ------------------------------------------------- VHMVKLLI
Mouse caspase-12         ---------------------------------------- MAARRTHERDPIYKIKGLA
Mouse caspase-11         ---------------------------------------- MAENKHPDKPLKVLEQLG
conserved amino acids[b]                                                    :. :

Human caspase-1          EGTINGLLDELLQTRVLNKEEMEKVKRENATVMDKTRALIDSVIPKGAQACQICITYICE
Human caspase-13[a]      KELISGLLDDFVEKNVLKLEEEEKKKIYDAKLQDKARVLVDSIRQKNQEAGQVFVQTFLN
Human caspase-4          KDFLTGVLDNLVEQNVLNWKEEEKKKYYDAKTEDKVRVMADSMQEKQRMAGQMLLQTFFN
Human caspase-5          KDVLHGVFNYLAKHDVLTLKEEEKKKYYDAKIEDKALILVDSLR-KNRVAHQMFTQTLLN
Human caspase-12         KTFLDGIFDDLMENNVLNTDEIHLIGKCLKFVVSNAENLVDDITETAQIAGKIFREHLWN
Mouse caspase-12         KDMLDGVFDDLVEKNVLNGDELLKIGESASFILNKAENLVENFLEKTDMAGKIFAGHIAN
Mouse caspase-11         KEVLTEYLEKLVQSNVLKLKEEDKQKFNNAERSDKRWVFVDAMKKKHSKVGEMLLQTFFS
conserved amino acids[b] :  :   :: : :  **. .*           .:   : : .  .   . ::    : .

Human caspase-1          EDSYLAGTLGLSADQ-------TSGNYLNMQDSQGVLSSFPAPQAVQDN-----PAMPTS
Human caspase-13[a]      ID----------------------------KNS----TSIKAPEETVAG-----PDESV-
Human caspase-4          ID----------------------------QIS----PNKKAHPNMEAG-----PPESG-
Human caspase-5          MD----------------------------QKI----TSVKPLLQIEAG-----PPESA-
Human caspase-12         SKKQLS------------------------------------------------------
Mouse caspase-12         SQEQLSLQFSNDEDDGPQKICTPSSPSESKRKVEDDEMEVNAGLAHESHLMLTAPHGLQS
Mouse caspase-11         VD----------------------------PGS----HHGEANLEMEE------PEE---
conserved amino acids[b]  .

Human caspase-1          SGSEGNVKLCSLEEAQRIWKQKSAEIYPIMDKSSRTRLALIICNEEFDSIPRRTGAEVDI
Human caspase-13[a]      - GSAATLKLCPHEEFLKLCKERAGEIYPIKERKDRTRLALIICNTEFDHMPPRNGAALDI
Human caspase-4          - ESTDALKLCPHEEFLRLCKERAEEIYPIKERNNRTRLALIICNTEFDHLPPRNGADFDI
Human caspase-5          - ESTNILKLCPREEFLRLCKKNHDEIYPIKKREDRRRLALIICNTKFDHLPARNGAHYDI
Human caspase-12         ----------------------- QIYPVMEKERRTCLASNIRNKEFNYLHNRNGSELDL
Mouse caspase-12         SEVQDTLKLCPRDQFCKIKTERAKEIYPVMEKEGRTRLALIICNKKFDYLFDRDNADTDI
Mouse caspase-11         -- SLNTLKLCSPEEFTRLCREKTQEIYPIKEANGRTRKALIICNTEFKHLSLRYGAKFDI
conserved amino acids[b]                          :***: . . *   *  * * :*. :  * .:  *:
```

FIGURE 1A

```
Human caspase-1                 TGMTMLLQNLGY SVDVKKNLTASD MTTELEAFAHRP EHKTSDSTFLVF MSHGIREGICGK
Human caspase-13[a]             LGMKQLLEGLGY TVEVEEKLTARD MESVLWKFAARE EHKSSDSTFLVF MSHGILDGICGT
Human caspase-4                 TGMKELLEGLDY SVDVEENLTARD MESALRAFATRP EHKSSDSTFLVL MSHGILEGICGT
Human caspase-5                 VGMKRLLQGLGY TVVDEKNLTARD MESVLRAFAARP EHKSSDSTFLVL MSHGILEGICGT
Human caspase-12                LGMXDLLENLGY SVGIKENLTAQE METALRQFAAHP EHQSSDSTFLVV MSHSILNGICGT
Mouse caspase-12                LNMQELLENLGY SVVLKENLTAQE METELMQFAGRP EHQSSDSTFLVF MSHGILEGICGV
Mouse caspase-11                IGMKGLLEDLGY DVVVKEELTAEG MESEMKDFAALS EHQTSDSTFLVL MSHGTLHGICGT
conserved amino acids[b]         .*  **:.*.* *  :::***  * : :  **    **::*******.***.  .****

Human caspase-1                 KHSEQVPDILQL NAIFNMLNTKNC PSLKDKPKVIII QACRGDSPGVVW FKDSVG-VSGNL
Human caspase-13[a]             MHSEEEPDVLPY DTIFRTFNNRNC LSLKDKPKVIIV QACRGANRGELW VSDSPP-ALADS
Human caspase-4                 VHDEKKPDVLLY DTIFQIFNNRNC LSLKDKPKVIIV QACRGANRGELW VRDSPA-SLEVA
Human caspase-5                 AHKKKKPDVLLY DTIFQIFNNRNC LSLKDKPKVIIV QACRGEKHGELW VRDSPA-SLAVI
Human caspase-12                KHWDQEPDVLHD DTIFEIFNNRNC QSLKDKPKVIIM QACRGNGAGIVW FTTDSGKASADT
Mouse caspase-12                KHRNKKPDVLHD DTIFKIFNNSNC RSLRNKPKILIM QACRGRYNGTIW VSTNKGIATADT
Mouse caspase-11                MHSEKTPDVLQY DTIYQIFNNCHC PGLRDKPKVIIV QACRGGNSGEMW IRESSK-PQLCR
conserved amino acids[b]         * .: **:*  ::*:. :*. :* .*::***::*:*****   * :*.  .

Human caspase-1                 SLP-TTEEFEDD AIKKAHIEKDFI AFCSSTPDNVSW RHPTMGSVFIGR LIEHMQEYACSC
Human caspase-13[a]             FSQ-SSENLEED AVYKTHVEKDFI AFCSSTPHNVSW RDIKKGSLFITR LITCFQKYAWCC
Human caspase-4                 SSQ-SSENLEED AVYKTHVEKDFI AFCSSTPHNVSW RDSTMGSIFITQ LITCFQKYSWCC
Human caspase-5                 SSQ-SSENLEAD SVCKIHEEKDFI AFCSSTPHNVSW RDRTRGSIFITE LITCFQKYSCCC
Human caspase-12                HGRLLQGNICND AVTKAHVEKDFI AFKSSTPR----------------------------
Mouse caspase-12                DEERVLSCKWNN SITKAHVETDFI AFKSSTPHNISW KVGKTGSLFISK LIDCFKKYCWCY
Mouse caspase-11                GVD-LPRNMEAD AVKLSHVEKDFI AFYSTTPHHLSY RDKTGGSYFITR LISCFRKHACSC
conserved amino acids[b]                 :::   * *.***** *:**

Human caspase-1                 DVEEIFRKVRFS FEQPDGRAQMPT TERVTLTRCFYL FPGH
Human caspase-13[a]             HLEEVFRKVQQS FEKPNVKAQMPT VERLSMTRYFYL FPGN
Human caspase-4                 HLEEVFRKVQQS FETPRAKAQMPT IERLSMTRYFYL FPGN
Human caspase-5                 HLMEIFRKVQKS FEVPQAKAQMPT IERATLTRDFYL FPGN
Human caspase-12                ---------SHS FETPNILTQLPT IERLSMTRYFYL FPGN
Mouse caspase-12                HLEEIFRKVQHS FEVPGELTQMPT IERVSMTRYFYL FPGN
Mouse caspase-11                HLFDIFLKVQQS FEKASIHSQMPT IDRATLTRYFYL FPGN
conserved amino acids[b]                 *** .   :*:** :* ::** *******:
```

FIGURE 1B

FIGURE 2A

```
hCaspase12      MADEKPSNGVLVHMVKLLIKTFLDGIFDDLMENNVLNTDEIHLIGKCLKFVVSNAENLVD
KW-Ap           MADEKPSNGVLVHMVKLLIKTFLDGIFDDLMENNVLNTDEIHLIGKCLKFVVSNAENLVD
KW-Bp           MADEKPSNGVLVHMVKLLIKTFLDGIFDDLMENNVLNTDEIHLIGKCLKFVVSNAE-LVD
KW-Cp           MADEKPSNGVLVHMVKLLIKTFLDGIFDDLMENNVLNTDEIHLIGKCLKFVVSNAENLVD
KW-Dp           MADEKPSNGVLVHMVKLLIKTFLDGIFDDLMENNVLNTDEIHLIGKCLKFVVSNAENLVD
KW-Ep           ------------------------------------------------------------
KW-Fp           ------------------------------------------------------------
KW-Hp           ------------------------------------------------------------
KW-Gp           ------------------------------------------------------------
KW-Ip           ------------------------------------------------------------
KW-Jp           MADEKPSNGVLVHMVKLLIKTFLDGIFDDLMENNVLNTDEIHLIGKCLKFVVSNAENLVD
KW-Kp           MADEKPSNGVLVHMVKLLIKTFLDGIFDDLMENNVLNTDEIHLIGKCLKFVVSNAENLVD

hCaspase12      DITETAQIAGKIFREHLWNSKKQLSSALLEIQGAQPSGKLKLCPHAHFHELKTKRADEIY
KW-Ap           DITETAQIAGKIFREHLWNSKKQLSSDISSDGEREANMPG--------------------
KW-Bp           DITETAQIAGKIFREHLWNSKKQLSSDISSDGEREANMPG--------------------
KW-Cp           DITETAQIAGKIFREHLWNSKKQLSSDISSDGEREANMPG--------------------
KW-Dp           DITETAQIAGKIFREHLWNSKKQLSSDISSDGEREANMPG--------------------
KW-Ep           ----------------------------------PSGKLKLCPHAHFHELKTKRADEIY
KW-Fp           --------------------------------AQPSGKLKLCPHAHFHELKTKRADEIY
KW-Hp           --------------------------------AQPSGKLKLCPHAHFHELKTKRADEIY
KW-Gp           --------------------------------AQPSGKLKLCPHAHFHELKTKRADEIY
KW-Ip           --------------------------------AQPSGKLKLCPHAHFHELKTKRADEIY
KW-Jp           DITETAQIAGKIFREHLWNSKKQLSSDISSDGEREANMPG--------------------
KW-Kp           DITETAQIAGKIFREHLWNSKKQLSSALLEIQGAQPSGKLKLCPHAHFHELKTKRADEIY
                                                  ..

hCaspase12      PVMEKERRTCLALNIRNKEFNYLHNRNGSELDLLGMRDLLENLGYSVVIKENLTAQEMET
KW-Ap           ------------LNIRNKEFNYLHNRNGSELDLLGMXDLLENLGYSVVIKENLTAQEMET
KW-Bp           ------------LNIRNKEFNYLHNRNGSELDLLGMXDLLENLGYSVVIKENLTAQEMET
KW-Cp           ------------LNIRNKEFNYLHNRNGSELDLLGMXDLLENLGYSVVIKENLTAQ----
KW-Dp           ------------LNIRNKEFNYLHNRNGSELDLLGMXDLLENLGYSVVIKENLTAQ----
KW-Ep           PVMEKERRTCLALNIRNKEFNYLHNRNGSELDLLGMRDLLENLGYSVVIKENLTA-----
KW-Fp           PVMEKERRTCLALNIRNKEFNYLHNRNGSELDLLGMXDLLENLGYSVVIKESLTAQEMET
KW-Hp           PVMEKERRTCLALNIRNKEFNYLHNRNGSELDLLGMXDLLENLGYSVVIKENLTAQ----
KW-Gp           PVMEKERRTCLALNIRNKEFNYLHNRNGSELDLLGMXDLLENLGYSVVIKENLTAQ----
KW-Ip           PVMEKERRTCLALNIRNKEFNYLHNRNGSELDLLGMXDLLENLGYSVVIKENLTAQEMET
KW-Jp           ------------LNIRNKEFNYLHNRNGSELDLLGMXDLLENLGYSVVIKENLTAQEME-
KW-Kp           PVMEKERRTCLALNIRNKEFNYLHNRNGSELDLLGMXDLLENLGYSVVIKENLTAQEMET
                          ************************ ************** ***

hCaspase12      ALRQFAAHPEHQSSDSTFLVFMSHGILNGICGTKHWDQEPDVLHDDTIFEIFNNRNCQSL
KW-Ap           ALRQFAAHPEHQSSDSTFLVFMSHSILNGICGTKHWDQEPDVLHDDTIFEIFNNRNCQSL
KW-Bp           ALRQFAAHPEHQSSDSTFLVFMSHSILNGICGTKHWDQEPDVLHDDTIFEIFNNRNCQSL
KW-Cp           ------------------------------------------------------------
KW-Dp           ------------------------------------------------------------
KW-Ep           ------------------------SILNGICGTKHWDQEPDVLHDDTIFEIFNNRNCQSL
KW-Fp           ALRQFAAHPEHQSSDSTFLVFMSHSILNGICGTKHWDQEPDVLHDDTIFEIFNNRNCQSL
KW-Hp           ------------------------------------------------------------
KW-Gp           ------------------------------------------------------------
KW-Ip           ALRQFAAHPEHQSSDSTFLAFMSHSILNRICGTKHWDQEPDVLHDDTIFEIFNNRNCQSL
KW-Jp           ---------------STFLVFMSHSILNGICGTKH------------------------
KW-Kp           ALRQFAAHPEHQSSDSTFLVFMSHSILNGICGTKHWDQEPDVLHDDTIFEIFNNRNCQSL
```

FIGURE 2B

```
hCaspase12      KDKPKVIIMQACRGNGAGIVWFTTDSGKASADTHGRLLQGNICNDAVTKAHVEKDFIAFK
KW-Ap           KDKPKVIIMQACRGNGAGIVWFTTDSGKASADTHGRLLQGNICNDAVTKAHVEKDFIAFK
KW-Bp           KDKPKVIIMQACRGNGAGIVWFTTDSGKASADTHGRLLQGNICNDAVTKAHVEKDFIAFK
KW-Cp           --------------GAGIVWFTTDSGKASADTHGRLLQGNICNDAVTKAHVEKDFIAFK
KW-Dp           --------------GAGIVWFTTDSGKASADTHGRLLQGNICNDAVTKAHVEKDFIAFK
KW-Ep           KDKPKVIIMQACRG----------------------------------------------
KW-Fp           KDKPKVIIMQAC------------------------------------------------
KW-Hp           --------------GAGIVWFTTDSGKASADTHGRLLQGNICNDAVTKAHVEKDFIAFK
KW-Gp           ----------------------------------------------------MVLGLFGSP
KW-Ip           KDKPK------------------------------------------------MVLGLFGSP
KW-Jp           ------------------------------------------------------------
KW-Kp           KDKPKVIIMQACRGNGAGIVWFTTDSGKASADTHGRLLQGNICNDAVTKAHVEKDFIAFK

hCaspase12      SSTPHNVSWRHETNGSVFISQIIYYFREYSWSHHLEEIFQKVQHSFETPNILTQLPTIER
KW-Ap           SSTPHNVSWRHETNGSVFISQIIYYFREYSWSHHLEEIFQKVQHSFETPNILTQLPTIER
KW-Bp           SSTP----------------------------------VQHSFETPNILTQLPTIER
KW-Cp           SSTPHNVSWRHETNGSVFISQIIYYFREYSWSHHLEEIFQKVQHSFETPNILTQLPTIER
KW-Dp           SSTP----------------------------------VQHSFETPNILTQLPTIER
KW-Ep           ------------------------------------------------------------
KW-Fp           ------------------------------------------------------------
KW-Hp           SSTPHNVSWRHETNGSVFISQIIYYFREYSWSHHLEEIFQKVQHSFETPNILTQLPTIER
KW-Gp           LTVEKPVQILMVGSCKVTSVMMLLQRLMWKRTSLLSNLPHHVQHSFETPNILTQLPTIER
KW-Ip           LTWKKPVQILMVGSCKVTSVMMLLQRFMWKRTSLLSNLPHHVQHSFETPNILTQLPTIER
KW-Jp           ------------------------------------------------------------
KW-Kp           SSTPHNVSWRHETNGSVFISQIIYYFREYSWSHHLEEIFQKVQHSFETPNILTQLPTIER

hCaspase12      LSMTRYFYLFPGN
KW-Ap           LSMTRYFYLFPGN
KW-Bp           LSMTRYFYLFPGN
KW-Cp           LSMTRYFYLFPGN
KW-Dp           LSMTRYFYLFPGN
KW-Ep           -------------
KW-Fp           -------------
KW-Hp           LSMTRYFYLFPGN
KW-Gp           LSMTRYFYLFPGN
KW-Ip           LSMTRYFYLFPGN
KW-Jp           -------------
KW-Kp           LSMTRYFYLFPGN
```

Human Caspase-12 compared to Mouse Caspase-12 with CARD domain, ICE-p20 domain, ICE-p10 domain and Active-site amino acids described.

```
hCaspase-12   MADEKPSNGVLVHMVKLLIKTFLDGIFDDLMENNVLNTDEIHLIGKCLKFVVSNAENLVD   60
mCaspase-12   MAARRTHERDPIYKIKGLAKDMLDGVFDDLVEKNVLNGDELLKIGESASFILNKAENLVE   60
              ** .:. :   :: :* * * :***:****:*:**** **:  **:. .*:.:*****:

hCaspase-12   DITETAQIAGKIFREHLWNSKKQLS----------------------------------   85
mCaspase-12   NFLEKTDMAGKIFAGHIANSQEQLSLQFSNDEDDGPQKICTPSSPSESKRKVEDDEMEVN  120
              :: *.:::*****  *: **::***        ↑auto catalytic

hCaspase-12   ----------SALLEIQGAQPSGKLKLCPHAHFHELKTKRADEIYPVMEKERRTCLALN   134
mCaspase-12   AGLAHESHLMLTAPHGLQSSEVQDTLKLCPRDQFCKIKTERAKEIYPVMEKEGRTRLALI   180
                        :*   :*.:: ...*****: :* ::**:**.********* ** ***
                        ↑calpain                ↑calpain

hCaspase-12   IRNKEFNYLHNRNGSELDLLGMRDLLENLGYSVVIKENLTAQEMETALRQFAAHPEHQSS   194
mCaspase-12   ICNKKFDYLFDRDNADTDILNMQELLENLGYSVVLKENLTAQEMETELMQFAGRPEHQSS   240
              *.**:*:**.:*:.:: *:*.*::**********:********** * ***.:******

hCaspase-12   DSTFLVFMSHGILNGICGTKHWDQEPDVLHDDTIFEIFNNRNCQSLKDKPKVIIMQACRG   254
mCaspase-12   DSTFLVFMSHGILEGICGVKHRNKKPDVLHDDTIFKIFNNSNCRSLRNKPKILIMQACRG   300
              *************:****.** :::**********:**** **:**::***::*******

hCaspase-12   NGAGI VWFTTDSGKASADTHGRLLQGNICNDAVTKAHVEKDFIAFKSSTPHNVSWRHETN   314
mCaspase-12   RYNGT IWVSTNKGIATADTDEERVLSCKWNNSITKAHVETDFIAFKSSTPHNISWKVGKT   360
              .  * :*.:*:.* *:***. . : .   *:::******.************:**:  ..
                              ↑auto catalytic

hCaspase-12   GSVFISQIIYYFREYSWSHHLEEIFQKVQHSFETPNILTQLPTIERLSMTRYFYLFP GN   373
mCaspase-12   GSLFISKLIDCFKKYCWCYHLEEIFRKVQHSFEVPGELTQMPTIERVSMTRYFYLFP GN   419
              **:***::*  *::*.*.:******:********.*. ***:*****:************
```

FIGURE 3

FIGURE 4A

```
h_Caspase-3      ------------------------------------------------------------
h_Caspase-7      ------------------------------------------------------------
h_Caspase-12     ------------------------------------------------------------MADE
m_Caspase-12     ------------------------------------------------------------MAAR
h_Caspase-4      ------------------------------------------------------------MAEG
h_Caspase-13     ------------------------------------------------------------MAED
h_Caspase-5      --------------MFKGILQSGLDNFVINHMLKNNVAGQTSIQTLVPNTDQKSTSVKKD
h_Caspase-1      ------------------------------------------------------------MAD
h_Caspase-6      ------------------------------------------------------------
h_Caspase-8      -----------------MDFSRNLYDIGEQLDSEDLASLKFLSLDYIPQRKQEPIKDALM
h_Caspase-10     MKSQGQHWYSSSDKNCKVSFREKLLIIDSNLGVQDVENLKFLCIGLVPNKKLEKSSSASD
h_Caspase-9      ------------------------------------------------------------MDE
h_Caspase-2      ---------------------------------------------MAADRGRRILGVCGM
h_Caspase-14     ------------------------------------------------------------

h_Caspase-3      ------------------------------------------------------------
h_Caspase-7      ------------------------------------------------------------
h_Caspase-12     KPSNGVLVHMVK----LLIKTFLDGI--FDDLMENNVLNTDEIHLIGKCL-KFVVSNAEN
m_Caspase-12     RTHERDPIYKIK----GLAKDMLDGV--FDDLVEKNVLNGDELLKIGESA-SFILNKAEN
h_Caspase-4      N-HRKKPLKVLE----SLGKDFLTGV--LDNLVEQNVLNWKEEEKKKYYD-AKTEDKVRV
h_Caspase-13     K-HNKNPLKMLE----SLGKELISGL--LDDFVEKNVLKLEEEEKKKIYD-AKLQDKARV
h_Caspase-5      N-HKKKTVKMLE----YLGKDVLHGV--FNYLAKHDVLTLKEEEKKKYYD-AKIEDKALI
h_Caspase-1      KVLKEKRKLFIR----SMGEGTINGL--LDELLQTRVLNKEEMEKVKREN-ATVMDKTRA
h_Caspase-6      ------------------------------------------------------------
h_Caspase-8      LFQRLQEKRMLEESNLSFLKELLFRINRLDLLITYLNTRKEEMERELQTPGRAQISAYRV
h_Caspase-10     VFEHLLAEDLLSEEDPFFLAELLYIIR-QKKLLQHLNCTKEEVERLLPTR--QRVSLFRN
h_Caspase-9      ADRRLLRRCRLR------LVEELQVDQLWDALLSSELFRPHMIEDIQRAGSGSRRDQARQ
h_Caspase-2      HPHHQETLKKNR----VVLAKQLLLSELLEHLLEKDIITLEMRELIQAKV--GSFSQNVE
h_Caspase-14     ------------------------------------------------------------

h_Caspase-3      ----------------MENTEN------SVDSK-SIKNLEPKIIH----GSE---------
h_Caspase-7      ----MADDQGCIEEQGVEDSANED----SVDAKPDRSSFVPSLFS----KKKKN------
```

FIGURE 4B

h_Caspase-12	**LVDDITETAQIAGKIFREHLWNS-----KKQLSSALL--EIQGAQ----PSG----K---**
m_Caspase-12	LVENFLEKTDMAGKIFAGHIANS-----QEQLSLQFSNDEDDGPQKICTPSSPSESKRKV
h_Caspase-4	MADSMQEKQRMAGQMLLQTFFNID----QISPNKKAHPNMEAGPP----ESGES------
h_Caspase-13	LVDSIRQKNQEAGQVFVQTFLNID----KNSTSIKAPEETVAGPD----ESVGS------
h_Caspase-5	LVDSLR-KNRVAHQMFTQTLLNMD----QKITSVKPLLQIEAGPP----ESAES------
h_Caspase-1	LIDSVIPKGAQACQICITYICEEDS---YLAGTLGLSADQTSGNYLNMQDSQGVLSSFPA
h_Caspase-6	----------------------------MSSASGLRRGHPAGGE-----EN---------
h_Caspase-8	MLYQISEEVSRSELRSFKFLLQEEISKCKLDDDMNLLDIFIEMEKRVILGEGKLDILKRV
h_Caspase-10	LLYELSEGIDSENLKDMIFLLKDSLP-KTEMTSLSFLAFLEKQGK---IDEDNLTCLEDL
h_Caspase-9	LIIDLETRGSQALPLFISCLEDTG----QDMLASFLRTNRQAAKLSKPTLENLTPVVLRP
h_Caspase-2	LLNLLPKRGPQAFDAFCEALRETKQGHLEDMLLTTLSGLQHVLPPLSCDYDLSLPFPVCE
h_Caspase-14	--

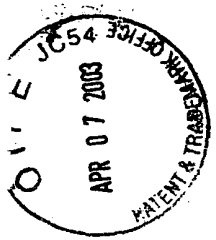
h_Caspase-3	--SMDS--GISLDN--------
h_Caspase-7	---------------------------------------VTMRS--IKTTRDRVPTY---
h_Caspase-12	**--------------------------------------LKLCPHAHFHELKTKRADE---**
m_Caspase-12	EDDEMEVNAGLAHES--HLM---LTAPHGLQSSEVQDTLKLCPRDQFCKIKTERAKE---
h_Caspase-4	-----------------------------------TDALKLCPHEEFLRLCKERAEE---
h_Caspase-13	-----------------------------------AATLKLCPHEEFLKLCKERAGE---
h_Caspase-5	-----------------------------------TNILKLCPREEFLRLCKKNHDE---
h_Caspase-1	PQAVQD-------------------NPAMPTSSGSEGNVKLCSLEEAQRIWKQKSAE---
h_Caspase-6	--MTETDAFYKREMFDPAE---
h_Caspase-8	CAQINKSLLKIINDY--EEFSKERSSSLEGSPDEFSNGEELCGVMTISDSPREQDSE---
h_Caspase-10	CKTVVPKLLRNIEKYKREKAIQIVTPPVDKEAESYQGEEELVSQTDVKTFLEALPQESWQ
h_Caspase-9	EIRK---------------------PEVLRPETPRPVDIGSGGFGDVGALESLRGNAD--
h_Caspase-2	SCPLYKKLR---------------LSTDTVEHSLDNKDGPVCLQVKPCTPEFYQTHFQ--
h_Caspase-14	--

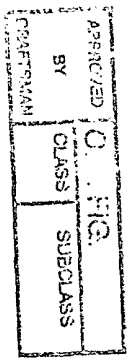
h_Caspase-3	---SYKMDYPEMGLCIIINNKN
h_Caspase-7	---QYNMNFEKLGKCIIINNKN
h_Caspase-12	**---IYPVMEKERRTCLALNIRN**
m_Caspase-12	---IYPVMEKEGRTRLALIICN
h_Caspase-4	---IYPIKERNNRTRLALIICN

FIGURE 4C

```
h_Caspase-13    -----------------------------------------IYPIKERKDRTRLALIICN
h_Caspase-5     -----------------------------------------IYPIKKREDRRRLALIICN
h_Caspase-1     -----------------------------------------IYPIMDKSSRTRLALIICN
h_Caspase-6     -----------------------------------------KYKMDHRRRGIALIFNHER
h_Caspase-8     -----------------------------------SQTLDKVYQMKSKPRGYCLIINNHN
h_Caspase-10    NKHAGSNGNRATNGAPSLVSRGMQGASANTLNSETSTKRAAVYRMNRNHRGLCVIVNNHS
h_Caspase-9     ----------------------------------------LAYILSMEPCGHCLIINNVN
h_Caspase-2     ----------------------------------------LAYRLQSRPRGLALVLSNVH
h_Caspase-14    ----------------------------------------MSNPRSLEEEKYDMSGARLA
                                                                  :

h_Caspase-3     FH-------KSTGMTSRSGTDVDAANLRETFRNLKYEVRNK-NDLTREEIVELMRDVSKE
h_Caspase-7     FD-------KVTGMGVRNGTDKDAEALFKCFRSLGFDVIVY-NDCSCAKMQDLLKKASEE
h_Caspase-12    K--------EFNYLHNRNGSELDLLGMRDLLENLGYSVVIKENLTAQEMETALRQFAAHP
m_Caspase-12    K--------KFDYLFDRDNADTDILNMQELLENLGYSVVLKENLTAQEMETELMQFAGRP
h_Caspase-4     T--------EFDHLPPRNGADFDITGMKELLEGLDYSVDVEENLTARDMESALRAFATRP
h_Caspase-13    T--------EFDHMPPRNGAALDILGMKQLLEGLGYTVEVEEKLTARDMESVLWKFAARE
h_Caspase-5     T--------KFDHLPARNGAHYDIVGMKRLLQGLGYTVVDEKNLTARDMESVLRAFAARP
h_Caspase-1     E--------EFDSIPRRTGAEVDITGMTMLLQNLGYSVDVKKNLTASDMTTELEAFAHRP
h_Caspase-6     FF-------WHLTLPERRRTCADRDNLTRRFSDLGFEVKCFNDLKAEELLLKIHEVSTVS
h_Caspase-8     FAKAREKVPKLHSIRDRNGTHLDAGALTTTFEELHFEIKPH-DDCTVEQIYEILKIYQLM
h_Caspase-10    F----------TSLKDRQGTHKDAEILSHVFQWLGFTVHIHNNVTKVEMEMVLQKQKCNP
h_Caspase-9     FCR------E-SGLRTRTGSNIDCEKLRRRFSSPHFMVEVKGDLTAKKMVLALLELAQQD
h_Caspase-2     FTG-------EKELEFRSGGDVDHSTLVTLFKLLGYDVHVLCDQTAQEMQEKLQNFAQLP
h_Caspase-14    L--------ILCVTKAREGSEEDLDALEHMFRQLRFESTMKRDPTAEQFQEELEKFQQAI
                                 *      *   :   :    :       .        :

                                 ↓
h_Caspase-3     D--HSKRSSFVCVLLSHGEEG-------IIFGTNG------PVDLKKITNFFRGDRCRSL
h_Caspase-7     D--HTNAACFACILLSHGEEN-------VIYGKDG------VTPIKDLTAHFRGDRCKTL
h_Caspase-12    E--HQSSDSTFLVFMSH_GILN-------GICGTKHWDQEPDVLHDDTIFEIFNNRNCQSL
m_Caspase-12    E--HQSSDSTFLVFMSHGILE-------GICGVKHRNKKPDVLHDDTIFKIFNNSNCRSL
h_Caspase-4     E--HKSSDSTFLVLMSHGILE-------GICGTVHDEKKPDVLLYDTIFQIFNNRNCLSL
h_Caspase-13    E--HKSSDSTFLVFMSHGILD-------GICGTMHSEEEPDVLPYDTIFRTFNNRNCLSL
```

FIGURE 4D






```
h_Caspase-5       E--HKSSDSTFLVLMSHGILE-------GICGTAHKKKKPDVLLYDTIFQIFNNRNCLSL
h_Caspase-1       E--HKTSDSTFLVFMSHGIRE-------GICGKKHSEQVPDILQLNAIFNMLNTKNCPSL
h_Caspase-6       ---HADADCFVCVFLSHGEGN-------HIYAYDA------KIEIQTLTGLFKGDKCHSL
h_Caspase-8       D--HSNMDCFICCILSHGDKG-------IIYGTDG-----QEAPIYELTSQFTGLKCPSL
h_Caspase-10      A--HADGDCFVFCILTHGRFG-------AVYSSDE-----ALIPIREIMSHFTALQCPRL
h_Caspase-9       ---HGALDCCVVVILSHGCQASHLQFPGAVYGTDG-----CPVSVEKIVNIFNGTSCPSL
h_Caspase-2       A--HRVTDSCIVALLSHGVEG-------AIYGVDG-----KLLQLQEVFQLFDNANCPSL
h_Caspase-14      DSREDPVSCAFVVLMAHGREG-------FLKGEDG-----EMVKLENLFEALNNKNCQAL
                     .    .    :::**           : .                :   :    * *

                                  ↓
h_Caspase-3       TGKPKLFIIQACRGT--ELDCGIETDSG-----VDDDMAC----------------HKIP
h_Caspase-7       LEKPKLFFIQACRGT--ELDDGIQADSG----PINDTDANPR--------------YKIP
h_Caspase-12      KDKPKVIIMQACRGN--GAGIVWFTTD-----SGKASADTHG-RLLQGNIC--NDAVTKA
m_Caspase-12      RNKPKILIMQACRGR--YNGTIWVSTN-----KGIATADTDEERVLS---CKWNNSITKA
h_Caspase-4       KDKPKVIIVQACRGA--NRGELWVRDSP----ASLEVASSQSSENLE------EDAVYKT
h_Caspase-13      KDKPKVIIVQACRGA--NRGELWVSDSP----PALADSFSQSSENLE------EDAVYKT
h_Caspase-5       KDKPKVIIVQACRGE--KHGELWVRDSP----ASLAVISSQSSENLE------ADSVCKI
h_Caspase-1       KDKPKVIIIQACRGD--SPGVVWFKDSV----GVSGNLSLPTTEEFE------DDAIKKA
h_Caspase-6       VGKPKIFIIQACRGN--QHDVPVIPLDV----VDNQTEKLDTNITEVD-----AASVYTL
h_Caspase-8       AGKPKVFFIQACQGDNYQKGIPVETDS-----EEQPYLEMDLS----------SPQTRYI
h_Caspase-10      AEKPKLFFIQACQGEEIQPSVSIEADALN---PEQAPTSLQ---------------DSI
h_Caspase-9       GGKPKLFFIQACGGEQKDHGFEVASTSPEDESPGSNPEPDATPFQEGLRTFDQLDAISSL
h_Caspase-2       QNKPKMFFIQACRGDETDRGVDQQDGKN----HAGSPGCEESDAGKE------KLPKMRL
h_Caspase-14      RAKPKVYIIQACRGEQRDPGETVGGDE-----IVMVIKDSP---------------QTI
                    ***: ::*** *      .

h_Caspase-3       VDA-DFLYAYSTAPGYYSWRNSKDGSWFIQSLCAMLKQYA-DKLEFMHILTRVNRKVATE
h_Caspase-7       VEA-DFLFAYSTVPGYYSWRSPGRGSWFVQALCSILEEHG-KDLEIMQILTRVNDRVARH
h_Caspase-12      HVEKDFIAFKSSTPHNVSWRHETNGSVFISQIIYYFREYS-WSHHLEEIFQ----KVQHS
m_Caspase-12      HVETDFIAFKSSTPHNISWKVGKTGSLFISKLIDCFKKYC-WCYHLEEIFR----KVQHS
h_Caspase-4       HVEKDFIAFCSSTPHNVSWRDSTMGSIFITQLITCFQKYS-WCCHLEEVFR----KVQQS
h_Caspase-13      HVEKDFIAFCSSTPHNVSWRDIKKGSLFITRLITCFQKYA-WCCHLEEVFR----KVQQS
h_Caspase-5       HEEKDFIAFCSSTPHNVSWRDRTRGSIFITELITCFQKYS-CCCHLMEIFR----KVQKS
h_Caspase-1       HIEKDFIAFCSSTPDNVSWRHPTMGSVFIGRLIEHMQEYA-CSCDVEEIFR----KVRFS
```

FIGURE 4E

```
h_Caspase-6       PAGADFLMCYSVAEGYYSHRETVNGSWYIQDLCEMLGKYG-SSLEFTELLTLVNRKVSQR
h_Caspase-8       PDEADFLLGMATVNNCVSYRNPAEGTWYIQSLCQSLRERCPRGDDILTILT----EVNYE
h_Caspase-10      PAEADFLLGLATVPGYVSFRHVEEGSWYIQSLCNHLKKLVPRMLKFLEKTM----EIRGR
h_Caspase-9       PTPSDIFVSYSTFPGFVSWRDPKSGSWYVETLDDIFEQWA-HSEDLQSLLL----RVANA
h_Caspase-2       PTRSDMICGYACLKGTAAMRNTKRGSWYIEALAQVFSERA-CDMHVADMLVKVN-ALIKD
h_Caspase-14      PTYTDALHVYSTVEGYIAYRHDQKGSCFIQTLVDVFTKRK---GHILELLT----EVTRR
                      * :   :      : :    *: :: :   : :      ..          :

h_Caspase-3       FESFSFDATFHAKKQIPCIVSMLTKE--LYFYH----
h_Caspase-7       FESQSDDPHFHEKKQIPCVVSMLTKE--LYFSQ----
h_Caspase-12      FET----PNILTQLPTIERLSMTRYF--YLFPGN---
m_Caspase-12      FEV----PGELTQMPTIERVSMTRYF--YLFPGN---
h_Caspase-4       FET----PRAKAQMPTIERLSMTRYF--YLFPGN---
h_Caspase-13      FEK----PNVKAQMPTVERLSMTRYF--YLFPGN---
h_Caspase-5       FEV----PQAKAQMPTIERATLTRDF--YLFPGN---
h_Caspase-1       FEQ----PDGRAQMPTTERVTLTRCF--YLFPGH---
h_Caspase-6       RVDFCKDPSAIGKKQVPCFASMLTKK--LHFFPKSN-
h_Caspase-8       VSN--KDDKKNMGKQMPQPTFTLRKK--LVFPSD---
h_Caspase-10      KRTVWG-AKQISATSLPTAISAQTPRPPMRRWSSVS-
h_Caspase-9       VSV------KGIYKQMPGCFNFLRKK--LFFKTS---
h_Caspase-2       REGYAPGTEFHRCKEMSEYCSTLCRH-LYLFPGHPPT
h_Caspase-14      MAEAELVQEGKARKTNPEIQSTLRKR--LYLQ-----
```

Legend:

- ↓ Active-site Residues
- * Identical Residues
- : Conservative Substitution
- . Allowable Substitution

CLUSTAL W (1.7) multiple sequence alignment

FIGURE 5A

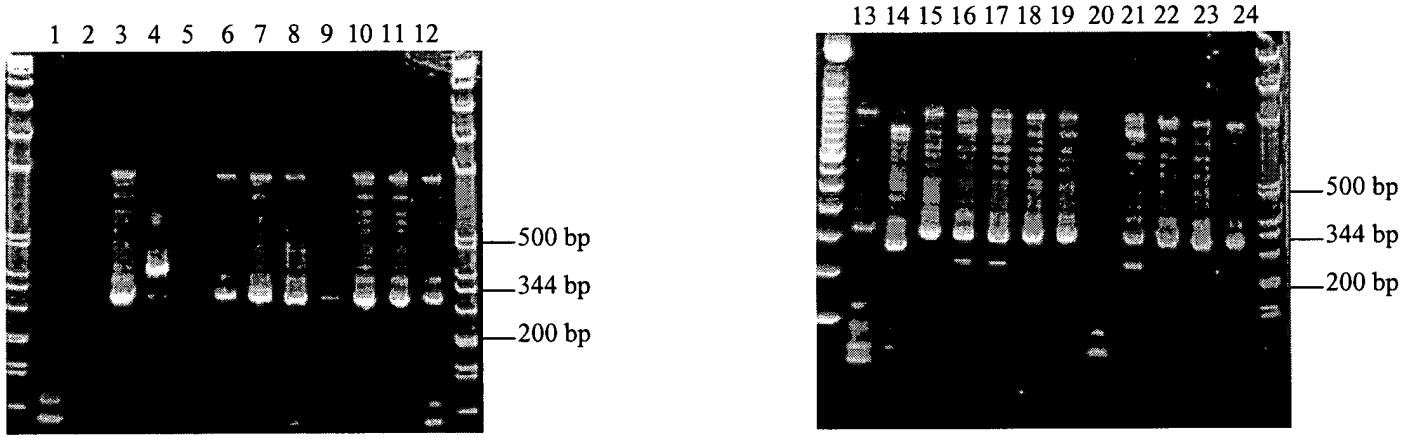
```
h_Caspase-4       ------------------------------------------MAEGN-HRKKPLKVLESL
h_Caspase-5       MFKGILQSGLDNFVINHMLKNNVAGQTSIQTLVPNTDQKSTSVKKDN-HKKKTVKMLEYL
h_Caspase-13      ------------------------------------------MAEDK-HNKNPLKMLESL
h_Caspase-12      ------------------------------------------MADEKPSNGVLVHMVKLL
h_Caspase-1       ------------------------------------------MADKVLKEKRKLFIRSM
                                                             :  .     .:. :

h_Caspase-4       GKDFLTGVLDNLVEQNVLNWKEEEKKKYYDAKTEDKVRVMADSMQEKQRMAGQMLLQTFF
h_Caspase-5       GKDVLHGVFNYLAKHDVLTLKEEEKKKYYDAKIEDKALILVDSLR-KNRVAHQMFTQTLL
h_Caspase-13      GKELISGLLDDFVEKNVLKLEEEEKKKIYDAKLQDKARVLVDSIRQKNQEAGQVFVQTFL
h_Caspase-12      IKTFLDGIFDDLMENNVLNTDEIHLIGKCLKFVVSNAENLVDDITETAQIAGKIFREHLW
h_Caspase-1       GEGTINGLLDELLQTRVLNKEEMEKVKRENATVMDKTRALIDSVIPKGAQACQICITYIC
                   :  : *::: : :  **. .* .          .:.  : *.:  .   * ::    :

h_Caspase-4       N-------------------------IDQISPNKKAHPNMEAG--PPESGESTDALKLCP
h_Caspase-5       N-------------------------MDQKITSVKPLLQIEAG--PPESAESTNILKLCP
h_Caspase-13      N-------------------------IDKNSTSIKAPEETVAG--PDESVGSAATLKLCP
h_Caspase-12      N-------------------------SKKQLSS--ALLEIQGA--QP-SGK----LKLCP
h_Caspase-1       EEDSYLAGTLGLSADQTSGNYLNMQDSQGVLSSFPAPQAVQDNPAMPTSSGSEGNVKLCS
                  :                              .   ..  .            *      :***.

h_Caspase-4       HEEFLRLCKERAEEIYPIKERNNRTRLALIICNTEFDHLPPRNGADFDITGMKELLEGLD
h_Caspase-5       REEFLRLCKKNHDEIYPIKKREDRRRLALIICNTKFDHLPARNGAHYDIVGMKRLLQGLG
h_Caspase-13      HEEFLKLCKERAGEIYPIKERKDRTRLALIICNTEFDHMPPRNGAALDILGMKQLLEGLG
h_Caspase-12      HAHFHELKTKRADEIYPVMEKERRTCLALNIRNKEFNYLHNRNGSELDLLGMRDLLENLG
h_Caspase-1       LEEAQRIWKQKSAEIYPIMDKSSRTRLALIICNEEFDSIPRRTGAEVDITGMTMLLQNLG
                    .  .: .:.  ****: .:. *  *** * * :*: :  *.*:  *: **  **:.*.

h_Caspase-4       YSVDVEENLTARDMESALRAFATRPEHKSSDSTFLVLMSHGILEGICGTVHDEKKPDVLL
h_Caspase-5       YTVVDEKNLTARDMESVLRAFAARPEHKSSDSTFLVLMSHGILEGICGTAHKKKKPDVLL
h_Caspase-13      YTVEVEEKLTARDMESVLWKFAAREEHKSSDSTFLVFMSHGILDGICGTMHSEEEPDVLP
h_Caspase-12      YSVVIKENLTAQEMETALRQFAAHPEHQSSDSTFLVFMSHGILNGICGTKHWDQEPDVLH
```

FIGURE 5B

```
h_Caspase-1       YSVDVKKNLTASDMTTELEAFAHRPEHKTSDSTFLVFMSHGIREGICGKKHSEQVPDILQ
                  *:*  :::*** :* : *  ** : **::*******:***** :****. * .: **:*

h_Caspase-4       YDTIFQIFNNRNCLSLKDKPKVIIVQACRGANRGELWVR-DSPASLEVASSQSSE-NLEE
h_Caspase-5       YDTIFQIFNNRNCLSLKDKPKVIIVQACRGEKHGELWVR-DSPASLAVISSQSSE-NLEA
h_Caspase-13      YDTIFRTFNNRNCLSLKDKPKVIIVQACRGANRGELWVS-DSPPALADSFSQSSE-NLEE
h_Caspase-12      DDTIFEIFNNRNCQSLKDKPKVIIMQACRGNGAGI VWFTTDSGKASADTHGRLLQGNICN
h_Caspase-1       LNAIFNMLNTKNCPSLKDKPKVIIIQACRGDSPGVVWFK-DSVGVSGNLSLPTTE-EFED
                   ::**. :*.:** **********:*****   * :*.  **            : ::

h_Caspase-4       DAVYKTHVEKDFIAFCSSTPHNVSWRDSTMGSIFITQLITCFQKYSWCCHLEEVFRKVQQ
h_Caspase-5       DSVCKIHEEKDFIAFCSSTPHNVSWRDRTRGSIFITELITCFQKYSCCCHLMEIFRKVQK
h_Caspase-13      DAVYKTHVEKDFIAFCSSTPHNVSWRDIKKGSLFITRLITCFQKYAWCCHLEEVFRKVQQ
h_Caspase-12      DAVTKAHVEKDFIAFKSSTPHNVSWRHETNGSVFISQIIYYFREYSWSHHLEEIFQKVQH
h_Caspase-1       DAIKKAHIEKDFIAFCSSTPDNVSWRHPTMGSVFIGRLIEHMQEYACSCDVEEIFRKVRF
                  *:: * * ******* ****.*****. . **:** .:*  :::*: . .: *:*:**:

h_Caspase-4       SFETPRAKAQMPTIERLSMTRYFYLFPGN
h_Caspase-5       SFEVPQAKAQMPTIERATLTRDFYLFPGN
h_Caspase-13      SFEKPNVKAQMPTVERLSMTRYFYLFPGN
h_Caspase-12      SFETPNILTQLPTIERLSMTRYFYLF PGN
h_Caspase-1       SFEQPDGRAQMPTTERVTLTRCFYLFPGH
                  *** *   :*:** ** ::** ******:
```

CARD domain ICE-P20 Domain ICE-P10 Domain **A**ctive-site **R**esidues

FIGURE 6



1. Brain 2. Heart 3. Kidney 4. Spleen 5. Liver 6. Colon 7. Lung 8. Small Intestine 9. Muscle 10. Stomach 11. Testis 12. Placenta 13. Pituitary 14. Thyroid gland 15. Adrenal gland 16. Pancreas 17. Ovary 18. Uterus 19. Prostate 20. PBL 21. Fetal brain 22. Fetal liver 23. Fat 24. Mammary gland

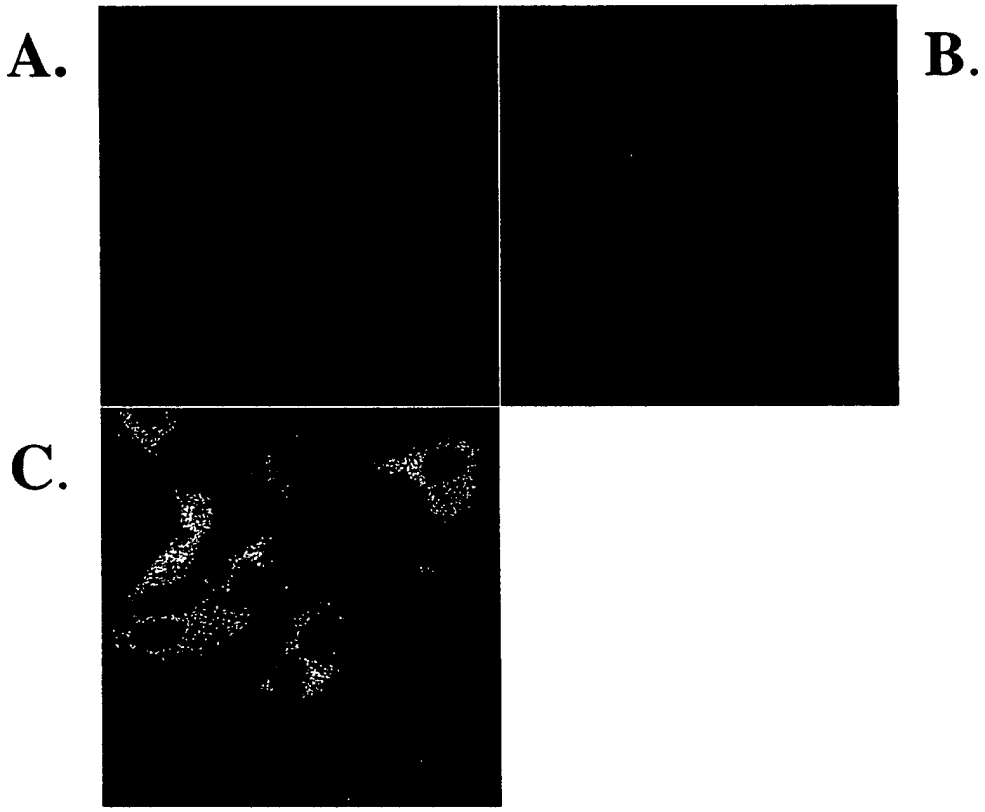


FIGURE 7

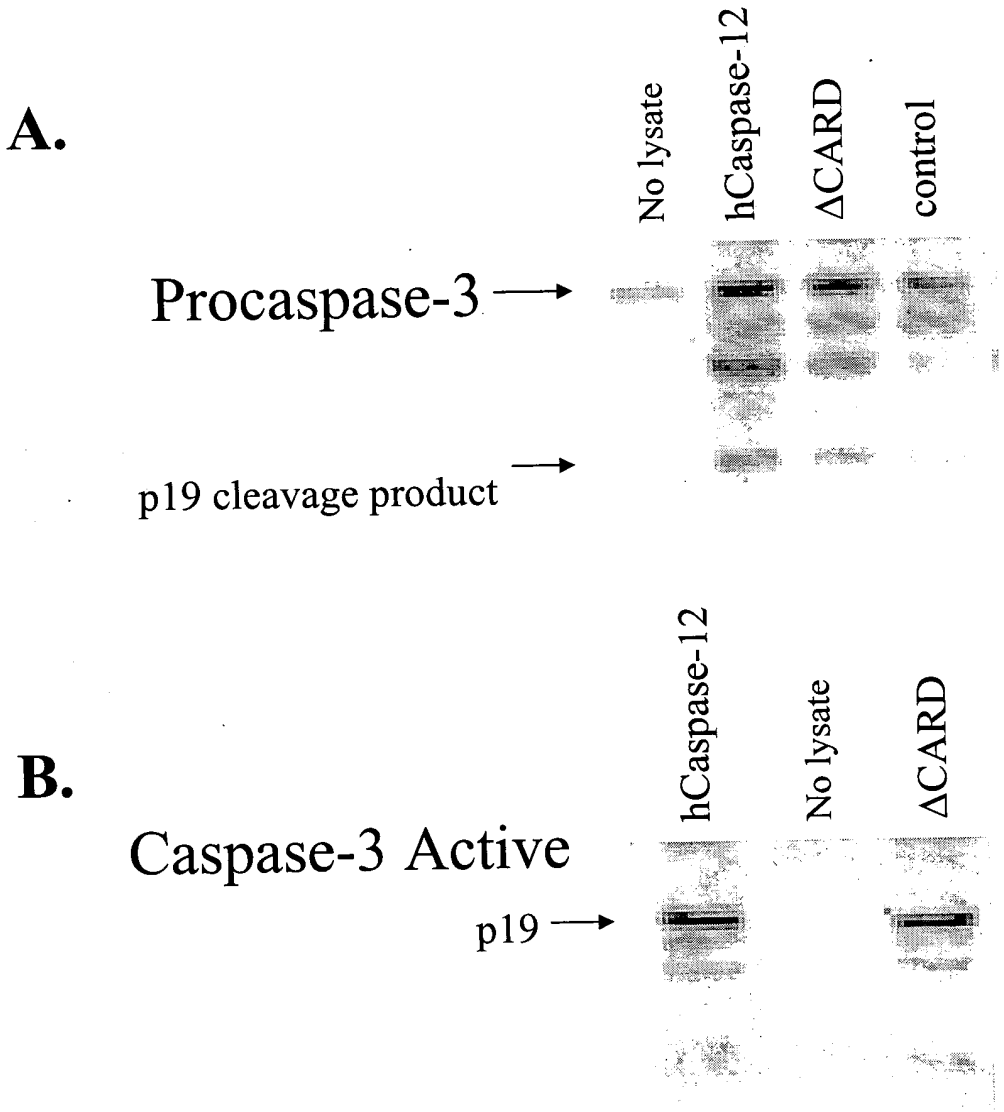


FIGURE 8

FIGURE 9

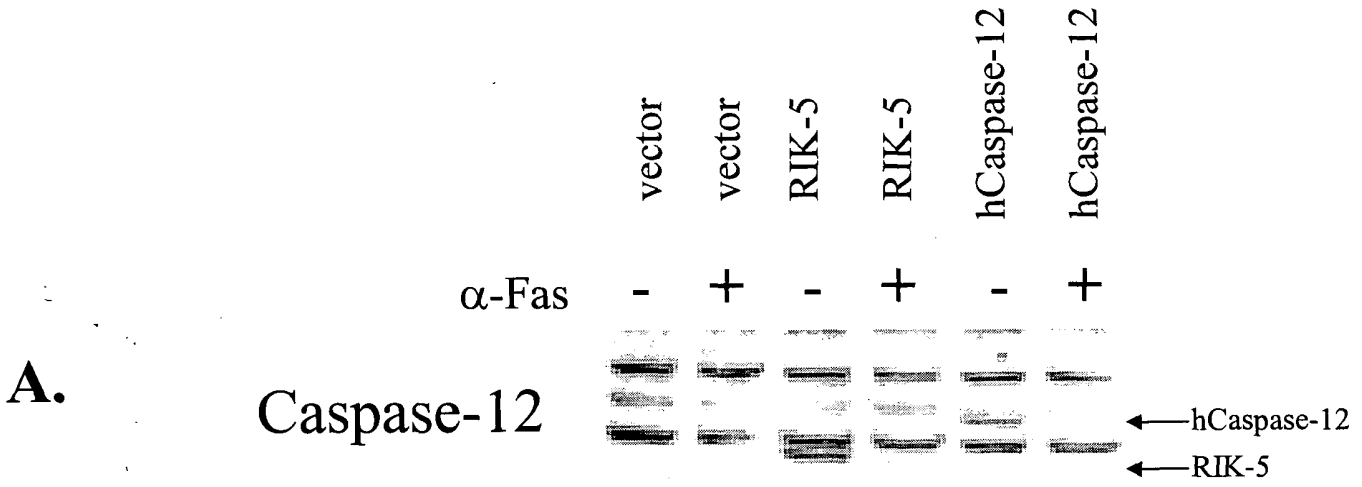
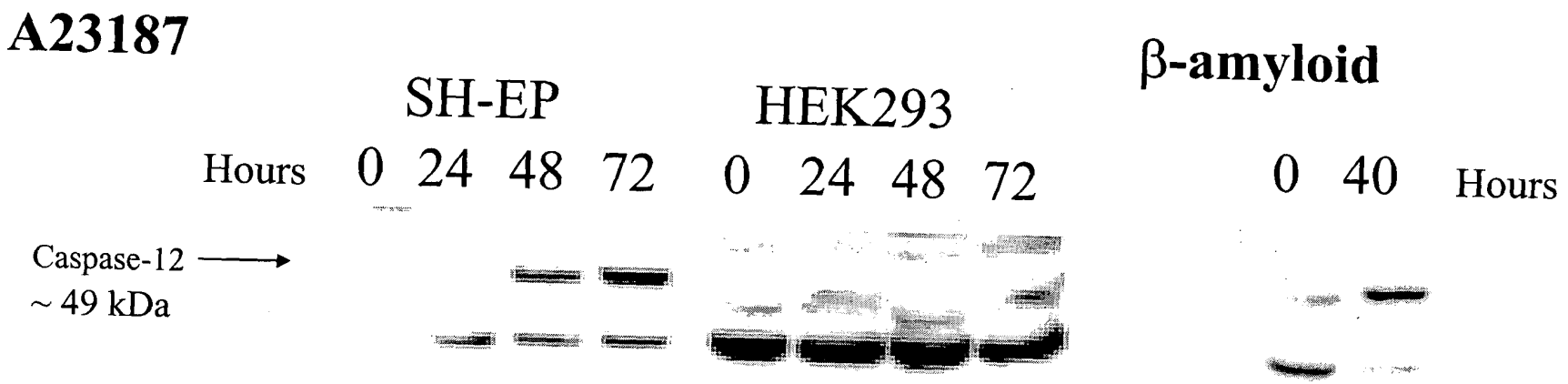


FIGURE 10



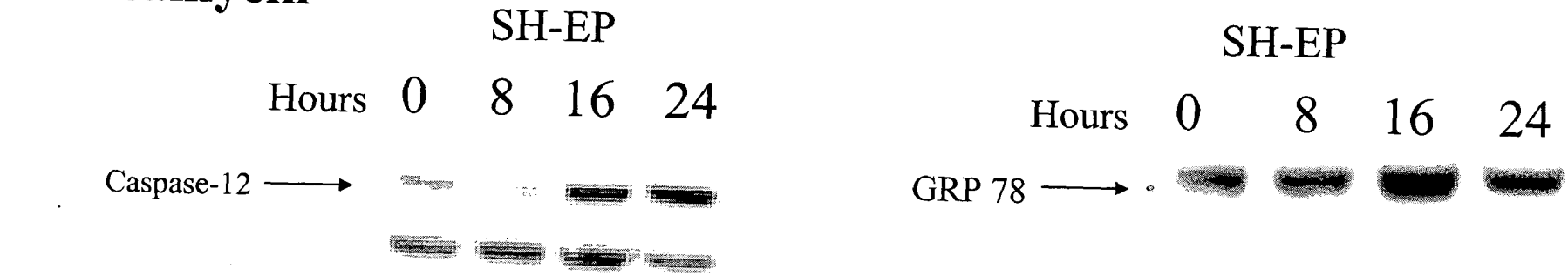


FIGURE 11

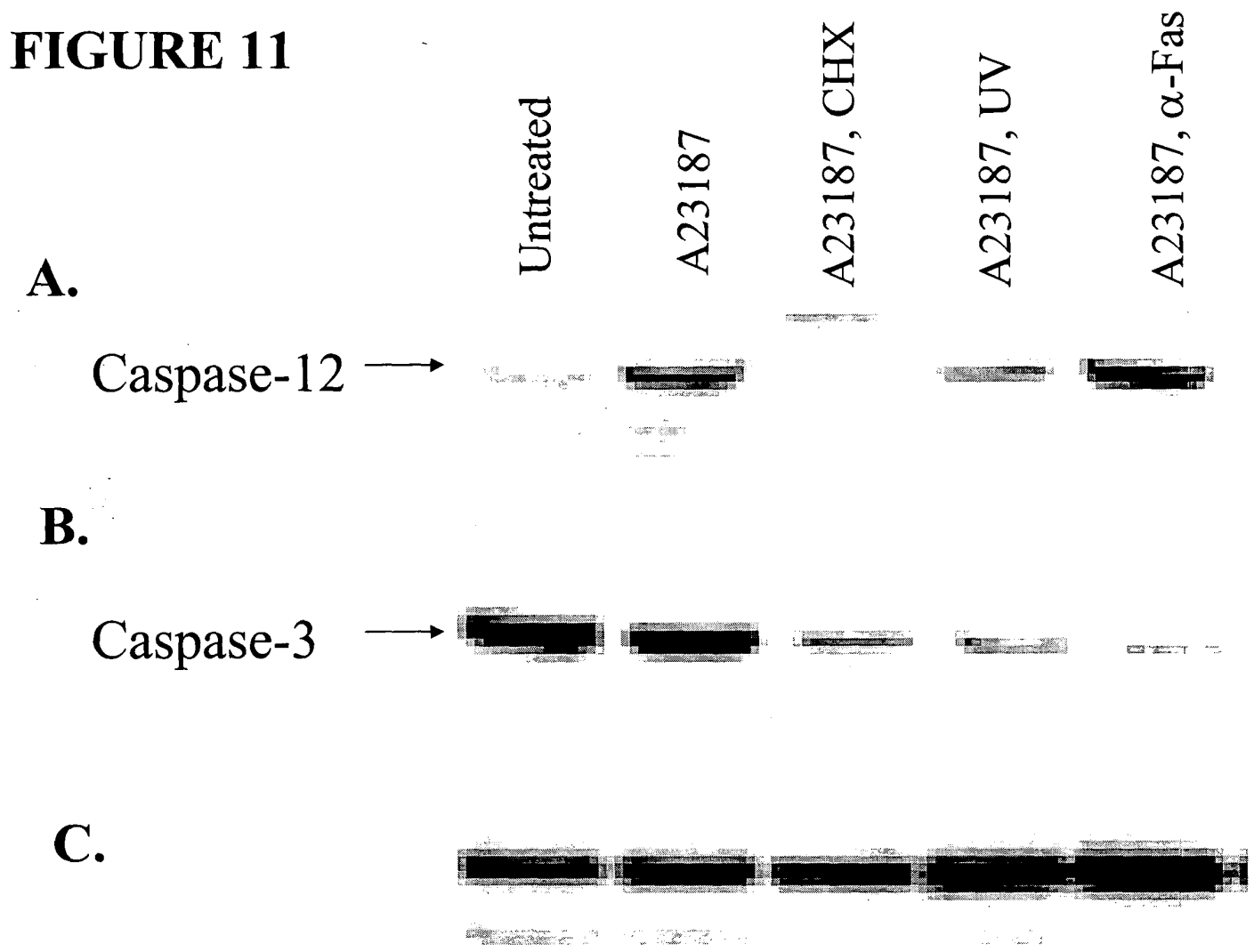
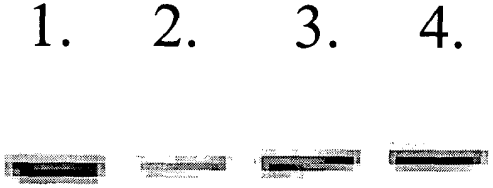


FIGURE 12

A.



B.

FIGURE 13